Modeling Chemical Fate and Metabolism for Computational Toxicology

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The goal of ORD's Computational Toxicology initiative is to develop the science for EPA to prioritize toxicity-testing requirements for chemicals subject to regulation. Many toxic effects, however, result from metabolism of parent chemicals to form metabolites that are much more toxic than the parent. Consequently, an accurate computerized simulator of metabolism is essential for meeting the objectives of the Computational Toxicology initiative. Because the liver is the primary organ for chemical metabolism, initial efforts will focus on the development of a metabolic simulator describing liver metabolism (i.e., a virtual liver). The primary goal of this research is to develop a computational system that will predict and prioritize metabolic pathways for the liver metabolism of organic chemicals.

The metabolic simulator must allow for prioritization of many competing metabolic pathways for parent chemicals. The prioritization process requires the integration of reliable rate data. When this data is absent, it is necessary to populate a database with metabolic rate constants based on: 1) experimentally measured values, 2) rate constants derived from mechanistic-based SPARC or QSAR models, and 3) advanced spectroscopic techniques (e.g., NMR) for measuring metabolic rate constants and identifying metabolites *in vivo* and *in vitro*. An initial challenge of this research is the selection of representative chemicals for study. To ensure focus on the highest priority chemicals, a workgroup specifically on metabolism will be formed. Such a workgroup will allow partners outside of ORD (e.g., OPPT, OSW and OW) an opportunity to have their priority questions answered in addition to the ORD research agenda.

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